

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050618 A2

(51) International Patent Classification⁷: **C07D 207/00**

(CH). VAN DER SCHAAF, Paul Adriaan [NL/CH];
Marsstrasse 17, CH-4123 Allschwill (CH).

(21) International Application Number:
PCT/US2003/038090

(74) Agents: **BRAINARD, Charles R.** et al.; Kenyon &
Kenyon, One Broadway, New York, NY 10004-1050 (US).

(22) International Filing Date:
26 November 2003 (26.11.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02406037.8 28 November 2002 (28.11.2002) EP
03405110.2 20 February 2003 (20.02.2003) EP

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants: **TEVA PHARMACEUTICAL INDUS-
TRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 1390,
49131 Petah Tiqva (IL). **TEVA PHARMACEUTICALS
USA INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090,
North Wales, PA 19454-1090 (US).

Published:

— *without international search report and to be republished
upon receipt of that report*

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BLAT-
TER, Fritz** [CH/CH]; Oerinstrasse 67, CH-4153
Reinach (CH). **SZELAGIEWICZ, Martin** [CH/CH];
Christoph-Merian-Strasse 1, CH-4142 Münchenstein

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CRYSTALLINE FORM

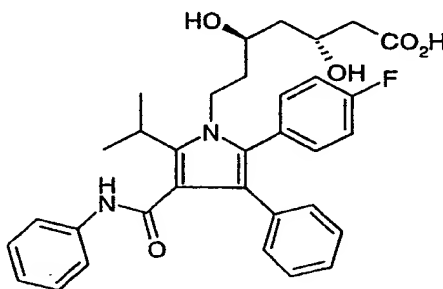
(57) Abstract: The present invention is directed to the novel polymorphic Form F of Atorvastatin calcium, processes for the prepa-
ration thereof and pharmaceutical compositions comprising this crystalline form.

WO 2004/050618 A2

Crystalline form

The present invention is directed to a crystalline form of Atorvastatin calcium, processes for the preparation thereof and pharmaceutical compositions comprising this crystalline form.

The present invention relates to a crystalline form of Atorvastatin calcium. Atorvastatin calcium is known by the chemical name, [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin has the following formula:



Atorvastatin calcium is an orally-active hypocholesterolaemic, a liver-selective HMG-CoA reductase inhibitor. Processes for the preparation of Atorvastatin calcium are described in US-A-5,273,995, US-A-5,298,627, US-A-6,087,511, US-A-6,274,740, WO-A-97/03960, WO-A-02/059087, WO-A-02/072073, and in the publications by P.L. Brower et al. in Tetrahedron Letters (1992), vol. 33, pages 2279-2282, K.L. Baumann et al. in Tetrahedron Letters (1992), vol. 33, pages 2283-2284 and A. Graul et al. in Drugs of the Future (1997), vol. 22, pages 956-968.

This calcium salt (2:1) is desirable since it enables Atorvastatin calcium to be conveniently formulated. The processes in the above mentioned patents and publications result in the preparation of amorphous Atorvastatin calcium.

The preparations of Atorvastatin calcium (2:1) described in WO-A-97/03958 and WO-A-97/03959 result in the isolation of crystalline Atorvastatin calcium with the polymorphic forms III, and I, II, and IV, respectively. WO-A-01/36384, WO-A-02/41834 and WO-A-02/43732 claim the preparation of crystalline Atorvastatin calcium with the polymorphic forms

V to XII, whereas WO-A-02/051804 claims the polymorphic forms A, B1, B2, C, D and E. However, there is still a need to produce Atorvastatin calcium in a reproducible, pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications. Furthermore, it is economically desirable that the product is stable for extended periods of time without the need for specialized storage conditions.

Surprisingly, there has now been found a novel crystalline form of Atorvastatin calcium salt (2:1), herein designated as Form F. This novel form of the present invention can be prepared in ecological friendly solvents and has a good thermal stability combined with good solubility characteristics.

Accordingly, the present invention is directed to the polymorphic Form F of Atorvastatin calcium salt (2:1).

Therefore, the present invention is directed to a crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 24.3 (s), 10.2 (s), 8.6 (s), 4.57 (vs), 4.26 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity.

More particularly, the crystalline polymorph F exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 32.3 (w), 24.3 (s), 16.5 (m), 13.0 (w), 11.4 (m), 10.2 (s), 8.6 (s), 7.0 (m), 6.4 (m), 5.16 (m), 4.96 (m), 4.57 (vs), 4.26 (m), 3.95 (m), 3.67 (m), 3.48 (m), 3.20 (w). The abbreviations in brackets mean: (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity.

Especially, the crystalline polymorph F exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 1 (vs = very strong intensity, s = strong intensity, m = medium intensity, w = weak intensity).

Table 1: d-spacings and 2 θ angles for Form F.

d-spacing [10^{-10} m]	Angle [2 θ]	Intensity
32.3	2.7	w
24.3	3.7	s
16.5	5.4	m
13.0	6.8	w
11.4	7.7	m
10.2	8.7	s
8.6	10.2	s
7.0	12.6	m
6.4	13.8	m
5.16	17.2	m
4.96	17.9	m
4.57	19.4	vs
4.26	20.8	m
3.95	22.5	m
3.67	24.2	m
3.48	25.5	m
3.20	27.8	w

The polymorphic Form F of Atorvastatin calcium is especially characterized by a powder X-ray diffraction pattern substantially as depicted in Figure 1.

Furthermore, the crystalline polymorph F exhibits a characteristic ^{13}C CP-MAS solid state NMR spectrum with chemical shifts (in parts per million, with peak intensity in arbitrary units in brackets) at 188.2 (2.5), 184.3 (2.2), 177.4 (2.8), 167.5 (2.9), 162.6 (2.4), 161.0 (3.9), 139.8 (6.5), 138.2 (4.3), 135.8 (5.1), 134.1 (4.0), 132.0 (8.4), 131.2 (7.3), 130.5 (14.0), 129.0 (9.5), 128.0 (6.6), 127.2 (4.6), 125.5 (2.9), 124.0 (4.9), 123.5 (4.7), 122.8 (4.8), 122.1 (6.2), 120.7 (5.4), 117.6 (4.1), 116.6 (4.1), 115.2 (3.6), 112.8 (1.6), 72.9 (4.8), 71.7 (5.2), 69.4 (6.5), 67.1 (4.9), 63.2 (0.7), 46.3 (10.4), 44.1 (12.6), 40.6 (7.6), 36.4 (0.7), 32.1 (3.8), 31.1 (1.3), 28.2 (5.3), 27.4 (9.0), 25.8 (11.2), 22.5 (3.7), 20.9 (4.2), 20.0 (4.8).

The polymorphic Form F of Atorvastatin calcium is especially characterized by a ^{13}C CP-MAS solid state NMR spectrum as depicted in Figure 2.

Furthermore, the present invention is directed to processes for the preparation of Form F of Atorvastatin calcium.

Form F can generally be prepared by adding Form A to a ketone solvent, especially acetone. It is preferred that the ketone solvent contains as a further solvent some water. The amount of water is preferably about 1 to 30%, more preferably about 5 to 20%, especially about 10 to 20% by volume of the suspension. It is preferred that the suspension is treated at temperatures between 10 and 60°C, preferably at temperatures of 20 to 40°C, especially for a longer periods of time, like 10 to 40 hours. It is further preferred that nucleation of Form F is induced at a temperature of 40 to 60°C, especially at about 60°C, and subsequent ripening and equilibration is performed at temperatures between 20 and 40°C. If desired, during the preparation process seeding with Form F can be carried out. Form F can, for example, be isolated by filtration and dried in air or in vacuum. The above mentioned process can also be carried out using another crystalline form or the amorphous form of atorvastatin calcium. Examples of other crystalline forms are Forms I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, A, B1, B2, C, D and E, which are disclosed and characterized in the references given hereinbefore. Preferred forms for this purpose are Form A (see for example WO-A-02/051804; last but one paragraph of page 2; page 4, last but one paragraph to page 5, first paragraph; Examples 2, 8 and 9; Fig. 2) or Form I (see for example WO-A-97/03959; table on page 4; page 20, line 9 to page 22, line 11; Example 1; Fig. 1). As to Form B1 see for example WO-A-02/051804; the paragraph bridging pages 2 and 3; page 5, second paragraph; Example 3; and Fig. 3). As to Form B2 see for example WO-A-02/051804; page 3, second paragraph; page 5, third paragraph; Example 4; and Fig. 3.

Form F can also be prepared from Atorvastatin lactone upon subsequent reaction with NaOH to form Atorvastatin sodium followed by reaction with CaCl_2 in a ketone solvent, especially in acetone. It is preferred that the ketone solvent contains as a further solvent some water. The amount of water is preferably about 1 to 30%. If desired, during the preparation process seeding with Form F can be carried out.

Form F can also be prepared directly from Atorvastatin lactone upon reaction with a calcium(II) salt, like Ca(OH)_2 or Ca(OAc)_2 , in a ketone solvent, especially in acetone. It is preferred that the ketone solution contains as a further solvent some water. The amount of

- 5 -

water is preferably about 1 to 30%. If desired, during the preparation process seeding with Form F can be carried out.

Form F can also be prepared by adding a concentrated solution of Atorvastatin calcium in an organic solvent, like tetrahydrofuran, to a ketone solvent, especially acetone. It is preferred that the ketone solution contains as a further solvent some water. The amount of water is preferably about 1 to 30%. If desired, during the preparation process seeding with Form F can be carried out.

As to the ketone solvent of the preparation processes given above it is preferred to use C₃-C₈ketones, especially acetone.

Another object of the present invention are crystalline forms of atorvastatin calcium which are essentially free of residual organic solvent. Preferred are Forms I to XII and A, B1, B2, C, D, E and F which are essentially free of residual organic solvent. Highly preferred are Forms B1, B2 and F, especially Form F. Forms I to XII and A, B1, B2, C, D, E are disclosed in the references given above. The following preparations of forms which are essentially free of residual organic solvents can be applied to any form of Atorvastatin calcium. It is preferred that the crystalline forms contain less than 0.5% by weight of residual organic solvent. Highly preferred are amounts of residual organic solvents of less than 5000 ppm, especially less than 2000 ppm. Most preferred are amounts of residual organic solvents of less than 400 ppm, especially less than 200 ppm. Examples of such residual organic solvents are acetone, ethylacetate, tetrahydrofuran, ethanol, methanol, acetonitrile and hexane.

Therefore, the present invention is directed to a crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which is essentially free of residual organic solvents and which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 24.3 (s), 10.2 (s), 8.7 (s), 4.80 (m), 4.56 (vs), 4.00 (m), 3.72 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity.

More particularly, the crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid

calcium salt (2:1) which is essentially free of residual organic solvents exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 31.9 (w), 24.3 (s), 16.3 (w), 13.1 (vw), 12.1 (w), 11.4 (m), 10.2 (s), 8.7 (s), 8.1 (vw), 7.1 (w), 6.9 (w), 6.5 (m), 5.98 (vw), 5.60 (vw), 5.21 (m), 5.00 (m), 4.80 (m), 4.56 (vs), 4.32 (w), 4.23 (m), 4.00 (m), 3.72 (m), 3.48 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity; (vw) = very weak intensity.

The crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which is essentially free of residual organic solvents is especially characterized by an X-ray powder diffraction pattern substantially as depicted in figure 3:

Furthermore, the crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which is essentially free of residual organic solvents exhibits a characteristic ¹³C CP-MAS solid state NMR spectrum with chemical shifts (in parts per million, with peak intensity in arbitrary units in brackets) at 187.7 (1.3), 184.6 (1.7), 177.7 (2.5), 167.5 (3.4), 162.8 (1.7), 161.1 (3.0), 143.6 (1.3), 140.0 (3.3), 139.3 (3.7), 138.0 (4.0), 137.1 (3.4), 136.0 (5.7), 134.1 (8.8), 132.0 (8.7), 131.3 (8.5), 130.2 (13.3), 129.5 (14.0), 127.9 (9.6), 126.8 (3.6), 125.3 (4.4), 123.1 (8.5), 120.5 (3.8), 117.5 (4.5), 115.3 (4.9), 112.8 (1.1), 72.7 (3.9), 71.5 (6.2), 69.3 (9.3), 67.2 (5.8), 46.3 (11.3), 44.4 (12.4), 41.3 (6.2), 40.6 (7.2), 34.7 (0.9), 32.0 (1.4), 30.8 (1.4), 28.2 (6.5), 27.3 (9.5), 25.9 (7.8), 21.1 (4.2), 20.3 (4.3).

The crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which is essentially free of residual organic solvents is especially characterized by a ¹³C CP-MAS solid state NMR spectrum substantially as depicted in figure 4.

It is preferred that the crystalline polymorphs F have a water content of up to 5% by weight (independently whether the polymorphs are essentially free of residual organic solvents or not).

- 7 -

Another object of the present invention are processes for the preparation of crystalline forms of atorvastatin calcium which are essentially free of residual organic solvent. Preferred are processes for the preparation of Forms I to XII and A, B1, B2, C, D, E and F which are essentially free of residual organic solvent. Highly preferred are processes for the preparation of Forms B1, B2 and F, especially Form F, which are essentially free of residual organic solvent. Forms I to XII and A, B1, B2, C, D, E are disclosed in the references given above. The following preparations of forms which are essentially free of residual organic solvents can be applied to any form of Atorvastatin calcium.

Particularly, the present invention is related to processes for the preparation of crystalline forms of atorvastatin calcium essentially free of residual organic solvent by exposing the crystalline form of atorvastatin calcium to an atmosphere with a defined relative air humidity. A relative air humidity of 5 to 100%, especially 40 to 80%, is preferred. A corresponding process for the preparation of Form F is preferred.

More particularly, atorvastatin calcium essentially free of residual organic solvent can be prepared by exposure to an inert gas flow with a defined relative air humidity (to exchange residual organic solvent with water). A relative air humidity of 5 to 100%, especially 40 to 80%, is preferred. A corresponding process for the preparation of Form F is preferred.

For example, Form F can be generally prepared essentially free of residual organic solvent by storage of this form in an atmosphere with a relative air humidity of 5 to 100%, preferably 40 to 80%, or by treating this form with a gas stream with a relative air humidity of 5 to 100%, preferably 40 to 80%.

The powder X-ray diffraction pattern as well as the ^{13}C CP-MAS solid state NMR spectrum of Form F essentially free of residual organic solvent may appear with slight deviations as compared to Form F containing residual organic solvent, compare Figure 3 and Figure 4 with Figure 1 and Figure 2, respectively.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form F, and a pharmaceutically acceptable carrier.

- 8 -

The polymorphic Form F may be used as single component or as mixtures with other polymorphic forms or the amorphous form of atorvastatin calcium.

As to Atorvastatin calcium it is preferred that it contains 25-100% by weight, especially 50-100% by weight of the novel form, based on the total amount of Atorvastatin calcium. Preferably, such an amount of the novel polymorphic form of Atorvastatin calcium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the present invention include powders, granulates, aggregates and other solid compositions comprising polymorphic Form F. In addition, the compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The

dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Atorvastatin calcium whereupon the properties that distinguish the solid form of Atorvastatin calcium are lost. However, the use of the novel form to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 1 to 100 mg of the novel Atorvastatin calcium form or mixtures with other forms of Atorvastatin calcium (including the amorphous form). More usually, the combined weight of the Atorvastatin calcium forms of a unit dosage are from 5 mg to 80 mg, for example 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius.

Example 1:

277 mg of Atorvastatin calcium Form A are added to 11 ml of a mixture of acetone and water (80:20 v/v). This suspension is stirred at ambient temperature for about ten minutes, leading to almost complete dissolution of Form A. When the resulting slightly turbid, opalescent

solution is stirred at 40°C for about 14 hours, a white precipitate is formed. This precipitate is separated by filtration and dried at 60°C for 2 hours. Yield: 153 mg (55%). Analysis by powder X-ray diffraction shows that the obtained sample is Atorvastatin calcium Form F as shown in Figure 1. Karl Fischer titration of the sample after X-ray diffraction reveals a water content of 2.0 %.

Example 2:

303 mg of Atorvastatin calcium Form A are added to a mixture of 10 ml acetone and 1 ml of water. This mixture is stirred at ambient temperature for about 15 minutes which leads to almost complete dissolution of the solid. The slightly turbid, opalescent solution/suspension is stirred at 40°C for 22 hours. Within this time a thick precipitate is formed. This suspension is thoroughly stirred at 50°C for about 15 minutes, then the mixture is cooled to 20°C while stirring is continued for another 4 hours. Then the suspension is filtrated and dried at 80°C for 3 hours (300 mbar). An X-ray powder diffraction study shows the product to be polymorphic Form F.

Example 3:

500 mg of Atorvastatin calcium Form I are suspended in 15 ml of acetone and water mixture (80:20 v/v). This suspension is shortly stirred at 60°C giving a clear solution which becomes immediately turbid. This turbid suspension is stirred for an additional 16 hours at 40°C. The resulting precipitate is filtered, washed with 2 ml of the acetone/water mixture and dried for 1 hour at 50°C/800 mbar. Yield 400 mg (80%). An X-ray powder diffraction study shows the product to be polymorphic Form F.

Example 4:

1.58 g of Atorvastatin calcium Form A are suspended in 44.2 g of a mixture of acetone and water (80:20), heated to 60°C and stirred for 3 hours. The white suspension formed is slowly cooled to 40°C, stirred for an additional 18 hours, slowly cooled to 20°C and stirred for an additional 2 hours. The suspension was filtered and dried at ambient temperatures with dry nitrogen. Yield 1.192 g. An X-ray powder diffraction study shows the product to be polymorphic Form F. Further analysis by ¹³C CP-MAS solid state NMR spectroscopy reveals a solid state NMR spectrum as shown in Figure 2. analysis by Karl Fischer titration reveals a water content of 1.3%, and analysis by GC-head space chromatography reveals an acetone content of 0.7%.

Example 5:

250 mg of Atorvastatin calcium Form F as obtained in example 4 was placed in a U-shaped glass tube in a oven at 60°C. This glass tube was purged with a nitrogen flow with a relative air humidity of ca. 50% for a period of 16 hours. Analysis by Karl Fischer titration reveals a water content of 2.5%, and analysis by GC-head space chromatography reveals an acetone content of less than 0.05%.

Example 6:

250 mg of Atorvastatin calcium Form F as obtained in example 4 was placed in a desiccator over a saturated NaCl solution at room temperature, i.e. in an atmosphere with a relative air humidity of 75%, for 44 hours. Analysis by Karl Fischer titration reveals a water content of 2.7%, and analysis by GC-head space chromatography reveals an acetone content of less than 0.05%. Further analysis by X-ray powder diffraction and ^{13}C CP-MAS solid state NMR spectroscopy shows that the crystal structure of Atorvastatin Form F was essentially retained under the given conditions, see Figures 3 and 4, respectively.

X-ray powder diffraction measurements were performed on a Philips 1710 powder X-ray diffractometer using Cu K α radiation (Cu K α_1 and Cu K α_2 at a ratio of 2, λ of Cu K α_1 = 1.54060, and λ of Cu K α_2 = 1.54447). The X-ray source is operated at 45 kV and 45 mA. Spectra are recorded at a step size of 0.02° with a counting time of 2.4 seconds per step. The accuracy of the 2 theta values of conventionally recorded powder X-ray diffraction patterns is generally +/- 0.2°. For sample preparation, about 40 mg of substance was prepared into circular shaped quartz sample holders of 0.5 mm depth and 10 mm width. The ^{13}C CP-MAS solid state NMR spectra were recorded on a Bruker Avance-600 NMR spectrometer operating at 600 MHz proton resonance frequency. Samples were filled into 4 mm rotors without further pretreatment. Bruker xwinnmr version 3.1 was used to acquire the spectra. All spectra were recorded with variable-amplitude (linear ramp) cross polarization from the protons and using high-power proton decoupling (100 KHz field strength using the XiX decoupling scheme). The MAS frequency was set to 15 KHz and stabilized to within 5 Hz. 3072 transients with 4096 complex data points each (acquisition time 41 ms) were added. The recycle delay was set to 3 sec leading to a measurement time of about 3 hours. The data analysis was carried out using MATLAB version 6.5. The first 200 complex data points of the acquired signal (FID) were Fourier transformed using a cosine-squared window

function and zero filling to 32768 data points leading to an optimized signal-to-noise ratio and spectral resolution. The digital resolution in the frequency domain is 1.53 Hz. The spectra were referenced to an external standard using uniformly $^{13}\text{C}/^{15}\text{N}$ labeled alanine by setting the resonance frequency of the C_α to 51.9 ppm. Under these measurement conditions and above described data evaluation the accuracy of the NMR shifts as presented is ± 0.05 ppm.

Brief description of the drawing

Figure 1 is a characteristic X-ray powder diffraction pattern for Form F.

Figure 2 is a characteristic ^{13}C CP-MAS solid state NMR spectrum of Form F.

Figure 3 is a characteristic X-ray powder diffraction pattern for Form F essentially free of residual organic solvent.

Figure 4 is a characteristic ^{13}C CP-MAS solid state NMR spectrum of Form F essentially free of residual organic solvent.

Claims

1. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 24.3 (s), 10.2 (s), 8.6 (s), 4.57 (vs), 4.26 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity.
2. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 32.3 (w), 24.3 (s), 16.5 (m), 13.0 (w), 11.4 (m), 10.2 (s), 8.6 (s), 7.0 (m), 6.4 (m), 5.16 (m), 4.96 (m), 4.57 (vs), 4.26 (m), 3.95 (m), 3.67 (m), 3.48 (m), 3.20 (w); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity.
3. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having an X-ray powder diffraction pattern substantially as depicted in figure 1.
4. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) which exhibits a characteristic ¹³C CP-MAS solid state NMR spectrum with chemical shifts (in parts per million, with peak intensity in arbitrary units in brackets) at 188.2 (2.5), 184.3 (2.2), 177.4 (2.8), 167.5 (2.9), 162.6 (2.4), 161.0 (3.9), 139.8 (6.5), 138.2 (4.3), 135.8 (5.1), 134.1 (4.0), 132.0 (8.4), 131.2 (7.3), 130.5 (14.0), 129.0 (9.5), 128.0 (6.6), 127.2 (4.6), 125.5 (2.9), 124.0 (4.9), 123.5 (4.7), 122.8 (4.8), 122.1 (6.2), 120.7 (5.4), 117.6 (4.1), 116.6 (4.1), 115.2 (3.6), 112.8 (1.6), 72.9 (4.8), 71.7 (5.2), 69.4 (6.5), 67.1 (4.9), 63.2 (0.7), 46.3 (10.4), 44.1 (12.6), 40.6 (7.6), 36.4 (0.7), 32.1 (3.8), 31.1 (1.3), 28.2 (5.3), 27.4 (9.0), 25.8 (11.2), 22.5 (3.7), 20.9 (4.2), 20.0 (4.8).
5. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium

salt (2:1) having a ^{13}C CP-MAS solid state NMR spectrum substantially as depicted in figure 2.

6. A crystalline polymorph of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)}$ which is essentially free of residual organic solvents.
7. A crystalline polymorph F of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)}$ which is essentially free of residual organic solvents.
8. A crystalline polymorph F of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)}$ essentially free of residual organic solvents which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (\AA) at 24.3 (s), 10.2 (s), 8.7 (s), 4.80 (m), 4.56 (vs), 4.00 (m), 3.72 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity.
9. A crystalline polymorph F of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)}$ essentially free of residual organic solvents which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (\AA) at 31.9 (w), 24.3 (s), 16.3 (w), 13.1 (vw), 12.1 (w), 11.4 (m), 10.2 (s), 8.7 (s), 8.1 (vw), 7.1 (w), 6.9 (w), 6.5 (m), 5.98 (vw), 5.60 (vw), 5.21 (m), 5.00 (m), 4.80 (m), 4.56 (vs), 4.32 (w), 4.23 (m), 4.00 (m), 3.72 (m), 3.48 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity; (vw) = very weak intensity.
10. A crystalline polymorph F of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)}$ essentially free of residual organic solvents having an X-ray powder diffraction pattern substantially as depicted in figure 3.
11. A crystalline polymorph F of $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophenyl})\text{-}\beta,\delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium$

- 15 -

salt (2:1) essentially free or residual organic solvents which exhibits a characteristic ^{13}C CP-MAS solid state NMR spectrum with chemical shifts (in parts per million, with peak intensity in arbitrary units in brackets) at 187.7 (1.3), 184.6 (1.7), 177.7 (2.5), 167.5 (3.4), 162.8 (1.7), 161.1 (3.0), 143.6 (1.3), 140.0 (3.3), 139.3 (3.7), 138.0 (4.0), 137.1 (3.4), 136.0 (5.7), 134.1 (8.8), 132.0 (8.7), 131.3 (8.5), 130.2 (13.3), 129.5 (14.0), 127.9 (9.6), 126.8 (3.6), 125.3 (4.4), 123.1 (8.5), 120.5 (3.8), 117.5 (4.5), 115.3 (4.9), 112.8 (1.1), 72.7 (3.9), 71.5 (6.2), 69.3 (9.3), 67.2 (5.8), 46.3 (11.3), 44.4 (12.4), 41.3 (6.2), 40.6 (7.2), 34.7 (0.9), 32.0 (1.4), 30.8 (1.4), 28.2 (6.5), 27.3 (9.5), 25.9 (7.8), 21.1 (4.2), 20.3 (4.3).

12. A crystalline polymorph F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic solvents having a ^{13}C CP-MAS solid state NMR spectrum substantially as depicted in figure 4.
13. A crystalline polymorph of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) according to any of claims 6 to 12 having a water content up to 5%.
14. A process for the preparation of a crystalline polymorph according to any of claims 1 to 13, wherein Atorvastatin calcium is added to a ketone solvent at temperatures between 10 and 60°C.
15. A process according to claim 14 in which Atorvastatin calcium Form A is used.
16. A process according to claim 14 in which the ketone is acetone.
17. A process according to claim 14 in which the ketone contains 1 to 30% water.
18. A process according to any of claims 14 to 17, wherein seeding is carried out with crystals of the crystalline polymorph according to any of claims 1 to 13.

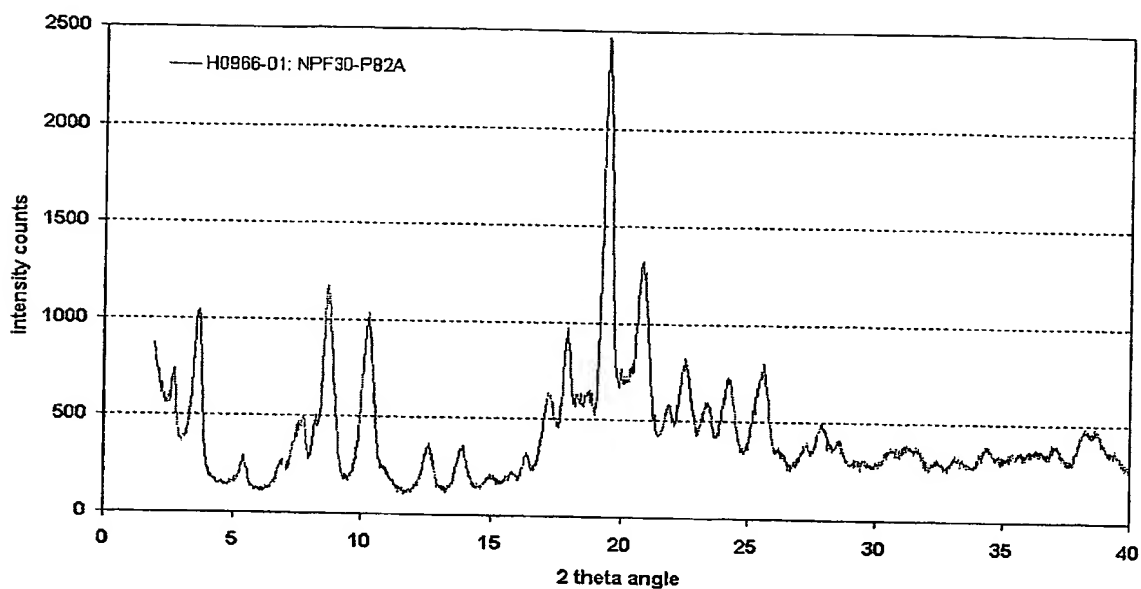
19. A process for the preparation of a crystalline polymorph according to any of claims 1 to 13, wherein Atorvastatin lactone in a ketone solvent is subsequently reacted with NaOH to form Atorvastatin sodium and then with CaCl_2 .
20. A process according to claim 19 in which the ketone is acetone.
21. A process according to claim 19 in which the ketone contains 1 to 30% water.
22. A process according to any of claims 19 to 21, wherein seeding is carried out with crystals of the crystalline polymorph according to any of claims 1 to 13.
23. A process for the preparation of a crystalline polymorph according to any of claims 1 to 13, wherein Atorvastatin lactone in a ketone solvent is reacted with a calcium(II) salt, preferably $\text{Ca}(\text{OH})_2$ or $\text{Ca}(\text{OAc})_2$.
24. A process according to claim 23 in which the ketone is acetone.
25. A process according to claim 23 in which the ketone contains 1 to 30% water.
26. A process according to any of claims 23 to 25, wherein seeding is carried out with crystals of the crystalline polymorph according to any of claims 1 to 13.
27. A process for the preparation of a crystalline polymorph according to any of claims 1 to 13, wherein a concentrated solution of Atorvastatin calcium in an organic solvent is added to a ketone solvent.
28. A process according to claim 27 in which the ketone is acetone, and the organic solvent is tetrahydrofuran.
29. A process according to claim 27 in which the ketone contains 1 to 30% water.
30. A process according to any of claims 27 to 29, wherein seeding is carried out with crystals of the crystalline polymorph according to any of claims 1 to 13.

31. A process for the preparation of any crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic solvents by exposing the organic solvent containing crystalline form to an atmosphere with a relative air humidity of 5 to 100%.
32. A process for the preparation of any crystalline form of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic solvents by equilibrating the organic solvent containing crystalline form in an inert gas flow with a relative air humidity of 5 to 100%.
33. A process according to claim 31 or 32 in which the relative air humidity is 40 to 80%.
34. A process for the preparation of crystalline form F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic by exposing the organic solvent containing crystalline form F to an atmosphere with a relative air humidity of 5 to 100%.
35. A process for the preparation of crystalline form F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic solvents by equilibrating the organic solvent containing form F in an inert gas flow with a relative air humidity of 5 to 100%.
36. A process for the preparation of crystalline form F of [R-(R*,R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) essentially free of residual organic solvents by equilibrating the organic solvent containing form F in a closed system under an atmosphere with a relative air humidity of 5 to 100%.
37. A process according to any of claims 34 to 36 in which the relative air humidity is 40 to 80%.

38. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to any of claims 1 to 13, and a pharmaceutically acceptable carrier.

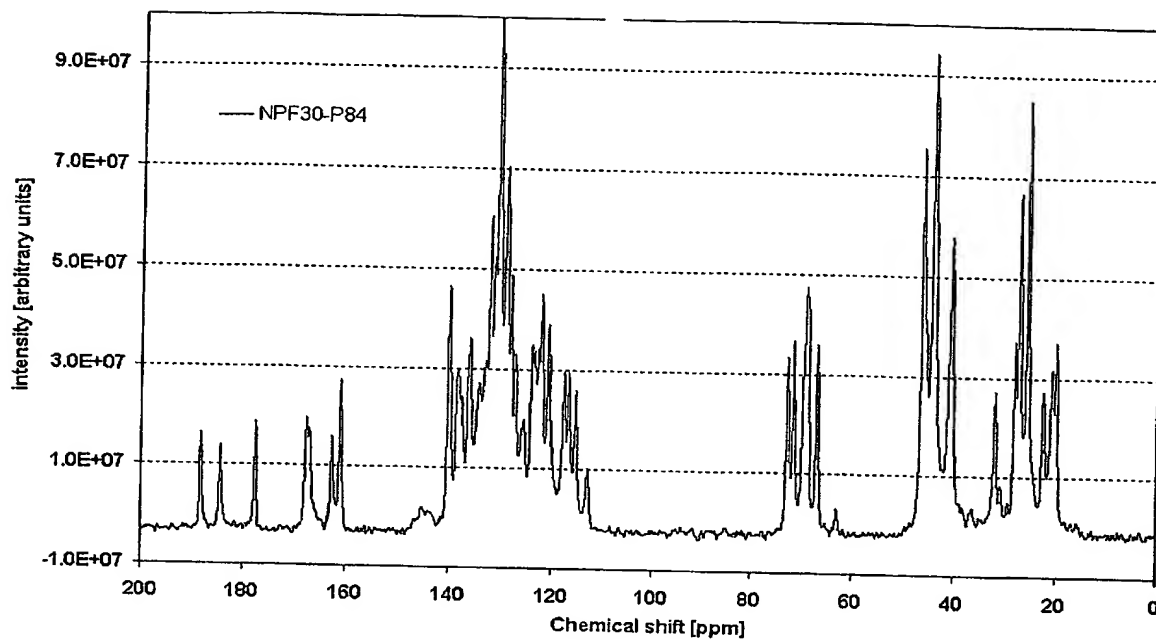
1 / 4

Figure 1:



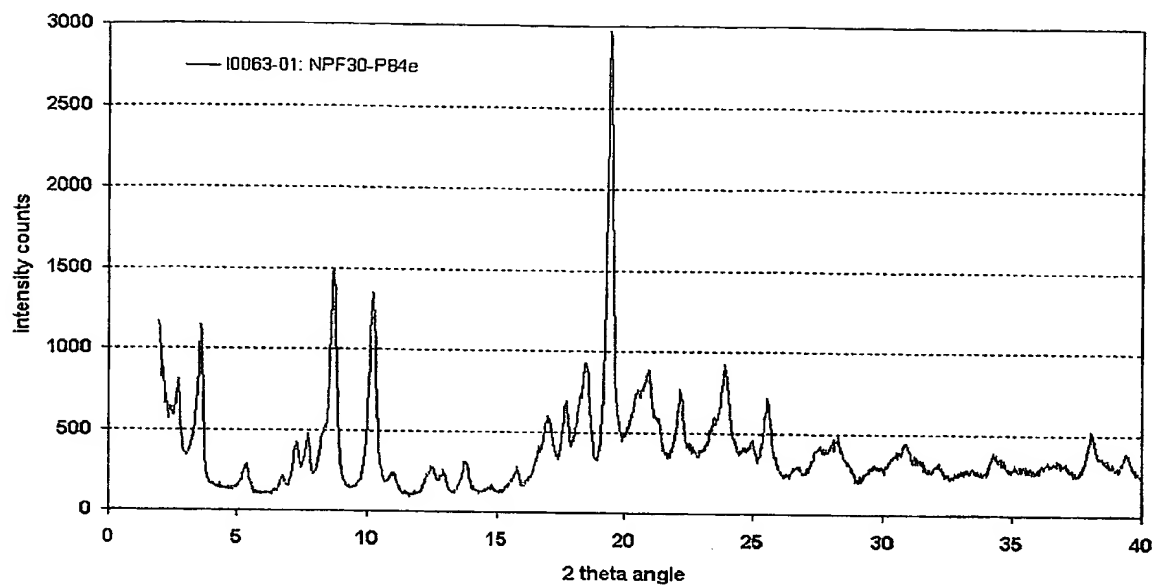
2 / 4

Figure 2:



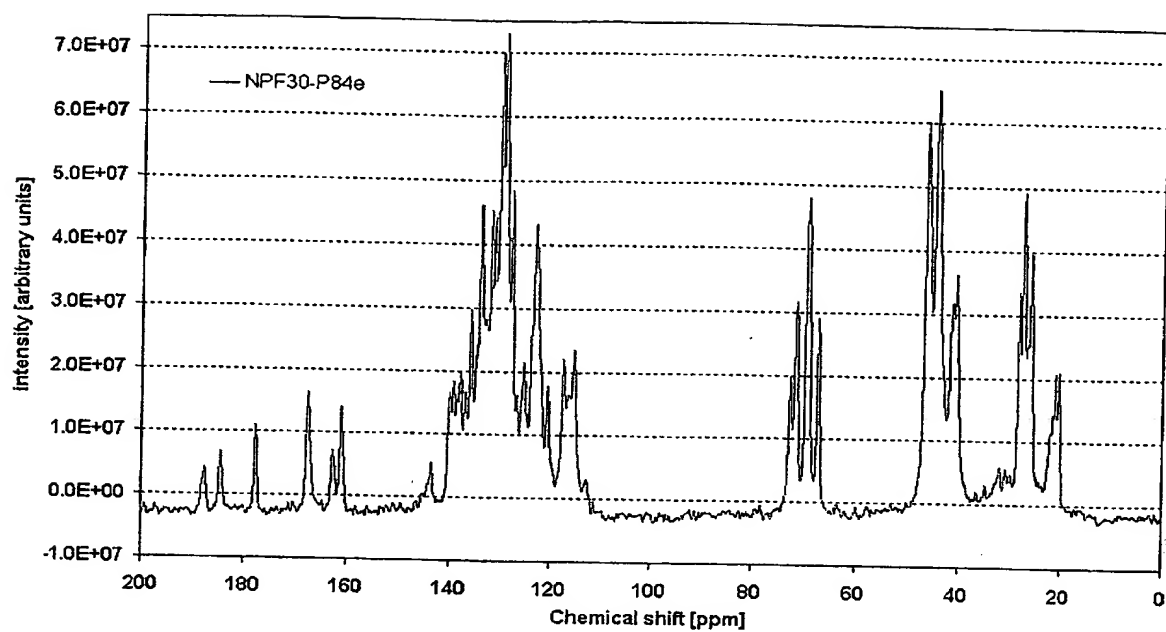
3 / 4

Figure 3:



4 / 4

Figure 4:



THIS PAGE BLANK (USPTO)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050618 A3

(51) International Patent Classification⁷: **C07D 207/34, A61K 31/40**

(74) Agents: **BRAINARD, Charles R. et al.**; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).

(21) International Application Number:
PCT/US2003/038090

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:
26 November 2003 (26.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(30) Priority Data:
02406037.8 28 November 2002 (28.11.2002) EP
03405110.2 20 February 2003 (20.02.2003) EP

(71) Applicants: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 1390, 49131 Petah Tiqva (IL). **TEVA PHARMACEUTICALS USA INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BLATER, Fritz** [CH/CH]; Oerinstrasse 67, CH-4153 Reinach (CH). **SZELAGIEWICZ, Martin** [CH/CH]; Christoph-Merian-Strasse 1, CH-4142 Münchenstein (CH). **VAN DER SCHAAF, Paul Adriaan** [NL/CH]; Marsstrasse 17, CH-4123 Allschwill (CH).

(88) Date of publication of the international search report:
15 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **CRYSTALLINE FORM F OF ATORVASTATIN HEMI-CALCIUM SALT**

(57) Abstract: The present invention is directed to the novel polymorphic Form F of Atorvastatin calcium, processes for the preparation thereof and pharmaceutical compositions comprising this crystalline form.

WO 2004/050618 A3

INTERNATIONAL SEARCH REPORT

Inter 1al Application No
PCT/US 03/38090

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/03958 A (WARNER LAMBERT CO ;MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) cited in the application claims 1-9	1-3
X	WO 97/03959 A (NAKAGAWA SHINSUKE ;HARASAWA KIKUKO (JP); MINOHARA KAZUO (JP); ICHI) 6 February 1997 (1997-02-06) cited in the application claims 1-29	1-10
X	WO 01/36384 A (TEVA PHARMA ;AYALON ARI (IL); NIDDAM VALERIE (IL); ROYTBAT SOFIA) 25 May 2001 (2001-05-25) cited in the application claims 1-16	1-3
	----- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

28 May 2004

Date of mailing of the international search report

09/06/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/38090

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/41834 A (TEVA PHARMA ;TEVA PHARMACEUTICALS USA INC (US)) 30 May 2002 (2002-05-30) cited in the application claims 1-17	1-3
X	WO 02/43732 A (ISHAI ETI ;SAMBURSKY GUY (IL); TEVA PHARMA (IL); ARONHIME JUDITH ()) 6 June 2002 (2002-06-06) cited in the application figures 1-13 examples 1,20,23,31,37,39 claims 1-146	1-10
X	WO 02/051804 A (SCHOENING KAI-UWE ;SZELAGIEWICZ MARTIN (CH); VAN DER SCHAAF PAUL A) 4 July 2002 (2002-07-04) cited in the application claims 1-16	1-3
X	WO 01/44181 A (TULLY WILLIAM ;CONNELL JOHN O (IE); MADIGAN EVELYN (IE); WARNER LA) 21 June 2001 (2001-06-21) claims 1-5	1-3
X	WO 01/44180 A (TULLY WILLIAM ;WARNER LAMBERT RES AND DEV IRE (IE)) 21 June 2001 (2001-06-21) claims 1-8	1-3
X	WO 02/057229 A (GANESH SAMBASIVAM ;MATHEW JOY (IN); BIOCON INDIA LTD (IN)) 25 July 2002 (2002-07-25) claims 1-10	1-3
P,X	WO 03/011826 A (NAGARAJU CHAKILAM ;REDDY M SATYANARAYANA (IN); REDDY SAGYAM RAJESW) 13 February 2003 (2003-02-13) claims 1-19	1-3
P,X	WO 03/004470 A (BYRN STEPHEN ROBERT ;COATES DAVID ANDREW (US); KRZYZANIAK JOSEPH F) 16 January 2003 (2003-01-16) page 52 - page 58 claims 1-15	1-10
P,X	WO 03/070702 A (MAIDAN-HANOCH DALIA ; TESSLER LIMOR (IL); TEVA PHARMA (IL); ARONHIME J) 28 August 2003 (2003-08-28) claims 1-46	1
E	WO 2004/022053 A (GREWAL MANMOHAN SINGH ; SURI SANJAY (IN); MOREPEN LAB LTD (IN); RAJ BA) 18 March 2004 (2004-03-18) claims 1-24	1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/38090

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703958	A	06-02-1997	AT 207465 T 15-11-2001
			AU 725368 B2 12-10-2000
			AU 6484196 A 18-02-1997
			BG 63629 B1 31-07-2002
			BG 102186 A 30-10-1998
			BR 9610567 A 06-07-1999
			CA 2220458 A1 06-02-1997
			CN 1190957 A ,B 19-08-1998
			CZ 9800123 A3 17-06-1998
			DE 69616358 D1 29-11-2001
			DK 848704 T3 04-02-2002
			EA 505 B1 28-10-1999
			EE 9800016 A 17-08-1998
			EP 0848704 A1 24-06-1998
			ES 2166456 T3 16-04-2002
			HK 1018053 A1 18-10-2002
			HR 960313 A1 30-04-1998
			HU 9901687 A2 28-10-1999
			ID 16158 A 11-09-1997
			IL 122162 A 14-07-1999
			JP 11509229 T 17-08-1999
			JP 3296563 B2 02-07-2002
			NO 980208 A 16-01-1998
			NZ 312906 A 22-12-2000
			PL 324532 A1 08-06-1998
			SK 5998 A3 06-05-1998
			TW 401399 B 11-08-2000
			WO 9703958 A1 06-02-1997
			US 6121461 A 19-09-2000
			ZA 9606045 A 04-02-1997
WO 9703959	A	06-02-1997	AT 208375 T 15-11-2001
			AU 725424 B2 12-10-2000
			AU 6484296 A 18-02-1997
			BG 63630 B1 31-07-2002
			BG 102187 A 30-10-1998
			BR 9609872 A 23-03-1999
			CA 2220018 A1 06-02-1997
			CN 1190955 A ,B 19-08-1998
			CZ 9800121 A3 14-10-1998
			DE 69616808 D1 13-12-2001
			DE 69616808 T2 29-05-2002
			DK 848705 T3 04-02-2002
			EA 474 B1 26-08-1999
			EE 9800015 A 17-08-1998
			EP 1148049 A1 24-10-2001
			EP 0848705 A1 24-06-1998
			ES 2167587 T3 16-05-2002
			HK 1018052 A1 01-11-2002
			HR 960339 A1 30-04-1998
			HU 9900678 A2 28-07-1999
			IL 122118 A 14-07-1999
			JP 11509230 T 17-08-1999
			JP 3296564 B2 02-07-2002
			NO 980207 A 16-01-1998
			NZ 312907 A 22-12-2000
			PL 324496 A1 25-05-1998
			PT 848705 T 28-02-2002

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/38090

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703959	A	SI 848705 T1 SK 6298 A3 TW 486467 B WO 9703959 A1 US 5969156 A ZA 9606044 A	30-04-2002 07-10-1998 11-05-2002 06-02-1997 19-10-1999 03-02-1997
WO 0136384	A 25-05-2001	AU 1617301 A CA 2392096 A1 CN 1423634 T CZ 20021642 A3 EP 1235799 A1 HR 20020429 A2 HU 0203257 A2 JP 2003514798 T SK 6742002 A3 WO 0136384 A1	30-05-2001 25-05-2001 11-06-2003 14-05-2003 04-09-2002 30-04-2004 28-01-2003 22-04-2003 02-05-2003 25-05-2001
WO 0241834	A 30-05-2002	AU 4150602 A CA 2426632 A1 CZ 20031495 A3 EP 1332130 A2 HU 0303765 A2 NO 20031986 A SK 6592003 A3 WO 0241834 A2 US 2002115709 A1	03-06-2002 30-05-2002 14-01-2004 06-08-2003 01-03-2004 02-05-2003 08-01-2004 30-05-2002 22-08-2002
WO 0243732	A 06-06-2002	AU 1792702 A BR 0115892 A CA 2429590 A1 EP 1363621 A1 NO 20032425 A WO 0243732 A1 US 2003212279 A1 US 2002183378 A1 AU 3289102 A CA 2427255 A1 CZ 20031595 A3 EP 1341785 A2 HU 0303555 A2 NO 20032200 A SK 7212003 A3 WO 0243667 A2 US 2002099224 A1	11-06-2002 28-10-2003 06-06-2002 26-11-2003 25-07-2003 06-06-2002 13-11-2003 05-12-2002 11-06-2002 06-06-2002 12-11-2003 10-09-2003 01-03-2004 24-06-2003 02-03-2004 06-06-2002 25-07-2002
WO 02051804	A 04-07-2002	CA 2431068 A1 CN 1483022 T CZ 20032019 A3 WO 02051804 A1 EP 1345896 A1 HU 0302519 A2 NO 20032758 A SK 9532003 A3 US 2003114686 A1	04-07-2002 17-03-2004 15-10-2003 04-07-2002 24-09-2003 29-12-2003 17-06-2003 06-04-2004 19-06-2003
WO 0144181	A 21-06-2001	AU 2214301 A CA 2391357 A1	25-06-2001 21-06-2001

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/38090

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0144181 A		EP 1242373 A1	25-09-2002
		HU 0203798 A2	28-03-2003
		WO 0144181 A1	21-06-2001
		JP 2003517039 T	20-05-2003
		US 2002161239 A1	31-10-2002
		US 2004024226 A1	05-02-2004
		ZA 200203649 A	20-12-2002
WO 0144180 A	21-06-2001	AU 2544001 A	25-06-2001
		CA 2388226 A1	21-06-2001
		EP 1237865 A1	11-09-2002
		HU 0203708 A2	28-03-2003
		WO 0144180 A1	21-06-2001
		JP 2003517038 T	20-05-2003
		US 2002156294 A1	24-10-2002
		ZA 200203648 A	10-02-2003
WO 02057229 A	25-07-2002	WO 02057229 A1	25-07-2002
		BR 0116785 A	09-03-2004
		CA 2436122 A1	25-07-2002
		CZ 20031946 A3	17-12-2003
		EP 1351963 A1	15-10-2003
		WO 02057274 A1	25-07-2002
		US 2004072893 A1	15-04-2004
WO 03011826 A	13-02-2003	CA 2454500 A1	13-02-2003
		EE 200400048 A	15-04-2004
		WO 03011826 A1	13-02-2003
WO 03004470 A	16-01-2003	CA 2450111 A1	16-01-2003
		EE 200300597 A	16-02-2004
		WO 03004470 A1	16-01-2003
		NZ 529557 A	19-12-2003
		US 6605729 B1	12-08-2003
		US 2004054193 A1	18-03-2004
WO 03070702 A	28-08-2003	WO 03070702 A1	28-08-2003
WO 2004022053 A	18-03-2004	WO 2004022053 A1	18-03-2004